

Efficacy of Acne Therapy Considering the Genotypes of the C174G Polymorphism in the *IL-6* Gene

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Abstract Acne vulgaris is a multifactorial inflammatory skin condition influenced by genetic, hormonal, microbial, and environmental factors. Recent studies have highlighted the role of cytokine gene polymorphisms, particularly in *interleukin-6* (IL-6), in modulating inflammatory responses and individual susceptibility to acne. To assess the efficacy of acne therapy in relation to the genotypes of the C174G polymorphism in the *IL-6* gene and to determine the potential of genotype-guided treatment strategies. A total of 133 patients with acne and 125 conditionally healthy individuals were genotyped for the C174G polymorphism in the *IL-6* gene using real-time PCR. Patients were divided into two treatment groups: one received standard therapy, and the other received a newly developed method involving pulsed dye laser, oral Toitriazoline, and topical agents. Treatment efficacy was evaluated in correlation with genotype distribution. The C allele frequency was significantly lower in the acne group compared to the control group (67.3% vs. 83.6%, $p = 0.01$), suggesting a protective role. The C/C genotype was associated with the highest rates of clinical remission, regardless of therapy type. The developed treatment method showed superior results in terms of remission and significant improvement, especially among carriers of the C/C genotype ($p < 0.01$). The *IL-6* C174G polymorphism contributes to acne susceptibility and treatment response. Genotype C/C is protective, while C/G and G/G are associated with increased risk. Therapy tailored to genetic background, particularly the use of the developed method in C/C carriers, may improve treatment outcomes.

Keywords Acne, Acne vulgaris, Gene polymorphism, IL-6 gene, Personalized therapy, Inflammation

1. Introduction

Acne (number: vulgare eels, eels, acne) - polymorphic multifactorial chronic disease of the sebaceous glands and hair follicles [8]. 80% of adolescents and young people have acne [1]. According to most researchers, acne occurs with similar frequency in both males and females, although more severe forms are more often observed in males [5,9].

The etiology and pathogenesis of acne are not fully studied. In modern dermatology, the etiology and pathogenesis of acne are considered as interrelated mechanisms: hormonal imbalance and hypersecretion of skin fat, change in its chemical composition, follicular hyperkeratosis, microbial colonization *Propionibacterium acnes* (*P. acnes*) and inflammation [10]. The authors indicate that the antigens of microorganisms (*P. acnes* and *P. granulosum*) contribute to the attraction of neutrophils, phagocytes into the duct of the sulfured follicle.

Neutrophils, on the one hand, stimulating the complement system, through Thall-like receptors (TLR2) promote the synthesis of interleukins (IL-8 and IL-12) and stimulate monocytes for the synthesis of IL-8, TNF- α , IL-1 β , IL-6) [2,3].

Studies by Polish researchers have shown that polymorphisms in cytokine genes such as C>T polymorphism in IL-1A may contribute to acne pathogenesis [6].

Under the influence of anti-inflammatory cytokines, an increase in the activity of cyclooxygenase occurs, as a result of which a mediator of the inflammatory process is formed - leukotriene B4 from arachidonic acid. Leukotriene B4 is able to activate monocytes, eosinophils, T-lymphocytes and other cells that secrete hydrolytic enzymes. The latter cause the destruction of the wall of the suet gland, which leads to its content entering into surrounding tissue and development of inflammatory process. Clinically, this manifests as papular-pustular and nodular lesions [4].

Therefore, different expression of the genes of interleukins can be associated with pathogenesis, clinical course and acne treatment.

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Received: Apr. 25, 2025; Accepted: May 20, 2025; Published: May 27, 2025

Published online at <http://journal.sapub.org/ajmms>

Several studies have shown a strong correlation between IL-6 levels and acne severity, suggesting IL-6 as a potential marker for disease progression and therapeutic response. [12,11,7]. For example, there was a significant difference in IL-6 levels in the group of patients with and without acne (95% DI 55.1 - 155.3, $p < 0.001$). The correlation analysis of IL-6 levels with acne severity was strictly positive ($r = 0.951$, $p < 0.001$) [7].

Therefore, the aim of this work was to analyze the efficacy of therapy taking into account the C174G (rs1800795) polymorphism genotypes of the IL6 gene.

2. Materials and Methods

We clinically monitored 133 acne patients aged 11 to 35 years. The average age was 19.8 ± 1.3 . There were 78 (58.6%) men and 55 (41.4%) women.

The distribution of patients by clinical forms of acne is presented in table 1 (according to Plewig G., et al. 2000).

Table 1. Distribution of patients by clinical forms of acne

| Clinical forms of acne | Women | | Men | | Total | |
|------------------------|-------|------|------|------|-------|------|
| | Abs. | % | Abs. | % | Abs. | % |
| Comedonal acne | 21 | 41.1 | 30 | 58.9 | 51 | 38.4 |
| Acne papulo-pustulosa | 28 | 42.4 | 38 | 57.6 | 66 | 49.6 |
| Acne conglobata | 6 | 37.5 | 10 | 62.5 | 16 | 12 |
| Overall | 55 | 41.4 | 78 | 58.6 | 133 | 100 |

The comedonal form is diagnosed in patients (38.4%), papulo-pustulosa - in (49.6%) and acne conglobata - in (12%). As can be seen from the data presented, there were more patients with male sex regardless of acne form and they often suffered with papulo-pustulosa form of disease.

Molecular genetic research was conducted in the scientific laboratory of the Department of Molecular Medicine and Cell Technologies at the Republican Scientific and Practical Center of Hematology.

This stage of the study included the following steps:

1. Collection of peripheral blood samples from patients and conditionally healthy donors.
2. Extraction of genomic DNA from peripheral blood lymphocytes using the "Ampli Prime RIBO-prep" kit ("AmpliSens", Russia). Real-time PCR analysis using

a kit for detecting the C174G polymorphism of the *IL-6* gene ("Литрекс", Moscow, Russia). Amplification was performed using the Rotor-Gene Q device (QIAGEN, Germany).

3. Statistical analysis of the data was carried out using the OpenEpi software package, version 9.2.

3. Results and Discussion

The analysis of allele and genotype frequency distribution of the C174G polymorphism in the *IL-6* gene revealed statistically significant differences between the study groups. The C allele was found significantly less frequently in the patient group — 67.3%, compared to 83.6% in the control group ($\chi^2 = 18.4$; $p = 0.01$; OR = 0.4; 95% CI: 0.27–0.61). These findings suggest a potential protective effect of the C allele against the studied condition.

The G allele was predominant in the patient group, accounting for 32.7%, compared to 16.4% in the control group ($\chi^2 = 18.4$; $p = 0.01$; OR = 2.5; 95% CI: 1.64–3.75). The distribution frequencies of alleles and genotypes of the C174G polymorphism in the *IL-6* gene among the acne patient group, its subgroups, and the control sample are presented in Table 2.

Regarding genotype distribution, statistically significant differences were observed in the homozygous C/C genotype of the *IL-6* C174G polymorphism between the patient and control groups, with frequencies of 48.1% and 71.2%, respectively ($\chi^2 = 14.2$; $p = 0.01$; OR = 0.4; 95% CI: 0.23–0.62). A non-significant trend toward a higher frequency of the heterozygous C/G genotype was observed among individuals with acne (38.3%) compared to the control group (24.8%) ($\chi^2 = 5.5$; $p = 0.03$; OR = 1.9; 95% CI: 1.11–3.21). The homozygous mutant G/G genotype was identified in 13.5% of patients in the main group, versus 4.0% in the control group. This may be considered a statistically significant risk factor for the development of inflammation in acne patients ($\chi^2 = 7.2$; $p = 0.01$; OR = 3.8; 95% CI: 1.43–9.87).

Thus, the C/C genotype of the *IL-6* C174G polymorphism appears to be protective, whereas the C/G genotype is associated with a 1.5-fold increased risk of developing acne, and the G/G genotype with a 3.4-fold increased risk.

All patients, considering the therapy they received, were divided into two groups. Both groups were comparable in terms of disease severity and duration.

Table 2. Allele and Genotype Frequency Distribution of the C174G Polymorphism in the *IL-6* Gene in the Patient Group, Subgroups with Acne, and the Control Sample

| N | | Allele frequency | | | | Genotype Frequency | | | | | |
|---|------------------------|------------------|------|----|------|--------------------|------|-----|------|-----|------|
| | | C | | G | | C/C | | C/G | | G/G | |
| | | n | % | n | % | n | % | n | % | n | % |
| 1 | Patient group (n =133) | 179 | 67,3 | 87 | 32,7 | 64 | 48,1 | 51 | 38,4 | 18 | 13,5 |
| 2 | Control group (n =125) | 209 | 83,6 | 41 | 16,4 | 89 | 71,2 | 31 | 24,8 | 5 | 4 |

The first group (47 patients) received conventional therapy in accordance with the standards for diagnosis and treatment established by the Ministry of Health of the Republic of Uzbekistan in the field of dermatovenereology (2019). Standard therapy included: vitamin therapy (ascorbic acid, B-group vitamins, tocopherol acetate, retinol acetate); antihistamines as indicated; and, in moderate to severe cases, systemic antibiotics. Topical antibiotics (such as erythromycin and azelaic acid) were also applied. Patients in this group used topical antibiotics externally.

The second group (36 patients) received a newly developed treatment method, which involved the use of a pulsed dye laser based on liquid dye technology, oral Toitriazoline (antioxidant) capsules, and external application of Clindamycin and benzoyl peroxide gel and ASW-ULTRA M-5+ tonic.

The treatment outcomes showed that among patients in the main group who received the developed method, clinical remission was achieved in 25 out of 36 patients (69.5%), significant improvement in 7 patients (19.4%), and improvement in 4 patients (11.1%). In the group that received conventional therapy, similar outcomes were observed as follows: clinical remission in 23 out of 47 patients (49.0%), significant improvement in 10 patients (21.2%), and improvement in 9 patients (19.1%).

The effectiveness of acne treatment according to the applied methods is presented in Table 3.

Table 3. Acne Treatment Effectiveness Based on the Applied Methods

| Treatment Outcomes | Main Group n=36 | | Conventional Therapy n=47 | |
|-------------------------|--------------------|---------|------------------------------|-------|
| | Abs. | % | Abs. | % |
| Clinical remission | 25 | 69.5%* | 23 | 49 |
| Significant improvement | 7 | 19.4%** | 10 | 21.2% |
| Improvement | 4 | 11.1%* | 14 | 29.8% |
| Worsening | - | - | - | - |

*- $p < 0.05$, **- $p > 0.05$

A particularly noteworthy aspect is the evaluation of treatment effectiveness in relation to the allele and genotype frequencies of the C174G polymorphism in the *IL-6* gene among acne patients.

An analysis of the effectiveness of conventional treatment based on the C174G genotypes of the *IL-6* gene revealed that patients with the favorable C/C genotype achieved the best clinical outcomes: clinical remission was observed in 11 patients (52.4%) and significant improvement in 6 patients (28.6%).

In contrast, among patients with the C/G genotype, clinical remission was achieved in 38% of cases, and significant improvement in 33.4% of cases.

For patients with the G/G genotype, treatment effectiveness was the lowest in comparison to the other genotypes: clinical remission occurred in only 20%, and significant improvement in 40% of patients.

It should be noted that a positive result—defined as either clinical remission or significant improvement—was achieved

in 81% of patients who received conventional therapy.

The treatment outcomes for acne patients receiving conventional therapy (n = 47), based on their *IL-6* C174G polymorphism genotypes, are presented in Table 4.

Table 4. Treatment Outcomes in Acne Patients According to *IL-6* C174G Gene Polymorphism Genotypes Receiving Conventional Therapy (n = 47)

| | Treatment Outcomes | C/C n=21 | | C/G n=21 | | G/G n=5 | |
|---|-------------------------|----------|------|----------|------|---------|------|
| | | Abs. | % | Abs. | % | Abs. | % |
| 1 | Clinical remission | 10 | 47.7 | 12 | 57.1 | 1 | 20.0 |
| 2 | Significant improvement | 4 | 19 | 4 | 19 | 2 | 40.0 |
| 3 | Improvement | 7 | 33.3 | 5 | 23.9 | 2 | 40.0 |
| | Overall | 21 | 100 | 21 | 100 | 5 | 100 |

The treatment outcomes of acne patients, depending on the genotypes of the *IL-6* C174G polymorphism who received the developed therapy method, showed that clinical remission was observed in 9 out of 13 patients (69.3%) with the C/C genotype, in 12 patients (63.1%) with the C/G genotype, and in 2 patients (50%) with the G/G genotype.

Significant improvement was achieved in 3 patients (23%) with the C/C genotype, 5 patients (26.3%) with the C/G genotype, and 1 patient (25%) with the G/G genotype.

A positive outcome, defined as either clinical remission or significant improvement, was most frequently observed in patients with the C/C genotype (92.3%).

The treatment outcomes of acne patients depending on the *IL-6* C174G polymorphism genotypes who received the developed therapy method are presented in Table 5.

Table 5. Treatment Outcomes in Acne Patients According to *IL-6* C174G Gene Polymorphism Genotypes Receiving the Developed Therapy Method (n = 36)

| Treatment Outcomes | C/C n=13 | | C/G n=19 | | G/G n=4 | |
|-------------------------|----------|------|----------|------|---------|-----|
| | Abs. | % | Abs. | % | Abs. | % |
| Clinical remission | 11 | 84.6 | 12 | 63.1 | 2 | 50 |
| Significant improvement | 1 | 7.7 | 5 | 26.3 | 1 | 25 |
| Improvement | 1 | 7.7 | 2 | 10.6 | 1 | 25 |
| Overall | 13 | 100 | 19 | 100 | 4 | 100 |

4. Conclusions

A comparative analysis of the study results revealed that the best clinical outcomes were observed in patients with the protective C/C genotype, regardless of the treatment method used. Moreover, in terms of clinical remission and the overall positive outcome (defined as clinical remission plus significant improvement), the proposed therapy method demonstrated a statistically significant advantage over the conventional treatment ($p < 0.01$).

Thus, the C174G polymorphism of the *IL-6* gene plays a role in the predisposition to and regulation of the inflammatory process in acne. The C/C genotype exerts a protective effect,

whereas the risk of developing acne increases 1.5-fold in carriers of the heterozygous C/G genotype and 3.4-fold in those with the homozygous G/G genotype. Treatment effectiveness is higher in carriers of the favorable genotype, regardless of the therapy method applied. The effectiveness of therapy was consistently higher among patients carrying the favorable C/C genotype, regardless of the treatment method applied. However, the developed treatment method which included pulsed dye laser therapy, oral Toitriazoline, and topical agents demonstrated a statistically significant improvement in clinical remission and overall positive outcomes ($p < 0.01$) compared to conventional therapy.

These results suggest that genotyping for the C174G polymorphism in the *IL-6* gene may serve as a valuable predictive tool in both assessing acne susceptibility and optimizing personalized treatment strategies.

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